EXHIBIT F

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DNA breaks (e.g. cl. 81, 83-87), since the recited methods are not accompanied by specific active process steps or limitations specifically directed to the process of non-homologous integration, nor are the method steps specifically directing "integrat[ion]" or "over-expressi[on]" under the uncontrolled conditions recited (see also 35 U.S.C. 102 rejection over Treco, as evidenced by Capecchi below).

Claim 92 recites the limitation "said vector construct" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 81, 83-88, 92, and 100-103 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In determining whether the specification provides an enabling disclosure for the claimed subject matter of claims 81, 83-88, 92, and 100-103, the factors for consideration are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine

screening. However, experimentation needed to practice the invention must not be undue experimentation....Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Factors that can be used in evaluating undue experimentation include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Claims 81-88 are drawn to methods for over-expressing endogenous genes *in vivo*. Upon evaluation of the specification in the instant application and in the parent applications, the only specific utility for the claimed method described in parent application 08/941,223 is in the context of *cells* to be used in vivo to provide that gene product in the intact animal (e.g. p. 8, lines 14-15; p. 16, lines 14-15; p. 48, lines 7-9) or for use of "[c]ells produced by this method...[to] be used...in vivo (e.g. for use in cell therapy)" (p. 29). The instant application essentially provides no further description or guidance concerning in vivo use of the claimed method beyond the limited descriptions alluded to in the '223' application (see e.g. p. 8, top paragraph; p. 10, lines 26-27; p. 36, lines 1-2, 18-19; p. 37, lines 3-4; p. 51, line 21 through p. 52, line 4; p. 52, lines 15-25; p. 54, lines 26-27; p. 71, lines 27-30). The specification fails to provide any written description or guidance for providing cells expressing endogenous gene products of the claimed method to an intact animal (e.g. or "desired amounts" thereto), except for reference to "use in cell therapy" as

described on p. 29, lines 24-25 and p. 54, lines 26-27 of the '223' and instant applications, respectively. Therefore, the only specific and substantial utility that could be gleaned from the instant disclosure is for use of the method in cell therapy which is interpreted to mean ex vivo gene therapy.

At the time the invention was made the technology for the successful use of *ex vivo* gene therapy was not routinely achieved (see for example, Kay et al., Proc. Natl. Acad. Sci. USA, 94:12744-12746, 11/97, p. 12746; Anderson, Nature, 392:25-30, 4/98, p. 25, top right column). Furthermore, at the time the invention was made, attempts at *ex vivo* gene therapy were essentially focused on transfer of transduced hematopoietic stem cells. While lethally irradiated mice can be reconstituted with retroviral vector transduced syngeneic bone marrow, such that the cells can provide genetically marked progeny persisting in blood and bone marrow over extended time periods, hematopoietic stem cells from large animals are much more refractory to gene transfer, cell engraftment, and sustained long-term expression coincident with HSC repopulation and expansion (Chu et al., J. Mol. Med., 76:184-192, 1998). Kay reported that the frequency of retrovirally transduced stem cells after transplantation in a human subject is only 0.001% of the endogenous stem cells, too low to result in detectable, stable engraftment (p. 12746, left column). A retroviral transduction efficiency leading to 0.01%-5% provirus positive circulating cells is too low to expect clinical improvement for the majority of human diseases associated with the hematopoietic system (Havenga et al., Stem Cells, 15:162-179, 1997). Since most HSCs are quiescent and do not support most types of retroviral gene transfer, many recent attempts have

employed (in addition to CD34+CD38- cell selection) the use of growth factors or cocultivation with genetically engineered stromal cell lines or preformed stromal layers (Chu et al., p. 187, top left paragraph). However, while the above approaches have demonstrated reasonably high levels of gene transfer into hematopoietic progenitors, gene transfer into HSCs assessed by *in vivo* reconstitution experiments in cats, dogs, and monkeys have failed to demonstrate clinically relevant levels of HSC gene transfer (p. 187, bottom left paragraph). In the majority of these latter studies fewer than 2% of hematopoietic cells and progenitors in the marrow and blood contained proviral sequences by 1 year posttransplant despite the use of *in vivo* cytoablation regimens, coculture with retroviral producer cell lines or engineered stromal cell lines, inclusion of growth factors during retroviral transduction, and/or the enrichment of hematopoietic progenitors and HSCs. Taken together, these results led Chu et al. to conclude that "currently available HSC gene-transfer protocols do not reliably transfer genes into HSCs with long-term repopulating capacity" (p. 189, last paragraph). Havenga lent a similar assessment in concluding that "for gene therapy to become a clinically relevant treatment, several problems have to be overcome...includ[ing] the identification of human PHSCs and the golden mixture of factors allowing *ex vivo* PHSC cycling and transduction without losing grafting potential" (p. 174, last paragraph).

The physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that the scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Given the lack of success in the *ex vivo* gene therapy art (i.e cell therapy), and the unpredictability of the physiological art, the need for clear and specific guidance, including working examples is underscored. However, no such guidance has been provided, beyond *the mere assertion of the use of the cells from the claimed method "for use in cell therapy"*. No further guidance is provided. For example, there is no guidance concerning requisite recombinant cell compositions, dosages, methodology for *in vivo* recombinant cell administration (and/or engraftment) in animals, nor guidance concerning selection of animals or patients in need of such compositions.

It is further noted that the instant disclosure does not provide any evidence of a specific, substantial, credible, or well-established utility for non-therapeutic *in vivo* administration of the recombinant cells of the claimed invention. Furthermore, any asserted use of the recited compositions or methods of the claimed invention for research purposes would raise issues of whether the utilities require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use. See , e.g., Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966) wherein a research utility was not considered a "substantial utility".

Considering the unpredictable and undeveloped state of the art as described above, it would likely require considerable experimentation to appropriately develop the claimed invention for *in vivo* cell therapy or *in vivo* cell transfer as recited in claims 81, 83-88, 92, and 100-103. This is particularly true given the state of the art, the nature of the invention, the unpredictability of the art, the scarcity of guidance and working examples in the specification, and the amount of experimentation necessary.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 81, 83, 86, 87, 92, and 100-102 are rejected under 35 U.S C. 102(e) as being anticipated by Sands et al. (U.S. 6,136,566, filed 10/4/96) and as further evidenced by Vasallo et al. (Bioch. Biophys. Res. Commun., 270(3):1036-1040, 4/00).

Sands discloses a method for producing an expression product of an endogenous cellular gene in vivo, comprising introducing a vector comprising a transcriptional regulatory sequence in